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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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NIXON & VANDERHYE
1100 NORTH GLEBE ROAD
8TH FLOOR
ARLINGTON, VA 22201-4714

EXAMINER	
YANG, NELSON C	
ART UNIT	**PAPER NUMBER**
1641	

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17

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/529,342	Applicant(s) CLARKE ET AL.	
	Examiner Nelson Yang	Art Unit 1641	

-- Th MAILING DATE of this communication app ars on the cover sheet with the correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) *18-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3, 6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of 1-41 in Paper No. 16 is acknowledged. The traversal is on the ground(s) that all of groups I-III do indeed incorporate a "special technical feature". This is not found persuasive because as discussed in the prior action mailed on September 24, 2003, in any application containing claims to different categories of invention, applicant is not entitled to any combination of categories having more than one method of use. Furthermore, when considering unity of invention, the term "special technical features" is defined as meaning those technical features that define a contribution which each of the inventions *considered as a whole*, makes over the prior art. In this situation, the intended use and limitations of the methods are not the same. Specifically, in group I, applicant recites the limitation of monitoring directly or indirectly for the species, a step which in not found in group II, while in group II, applicant recites the limitation that the species modulate the activity of said cell type of interest, a limitation not found in groupI.In addition, the lipid vesicle particle of group III is not commensurate in scope with either of the methods of groups I or II (group III does not recite the limitation of monitoring for the species nor the limitation of modulating the activity of said cell type of interest), and the special technical feature of group III is not, in fact, novel over the prior art.

2. The requirement is still deemed proper and is therefore made FINAL.

Specification

3. Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of **37 C.R.F. §§ 1.821-1.825**, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Sequence Requirements

4. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the Raw Sequence Listing Error Report.

5. Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply.

APPLICANT IS GIVEN THE TIME ALLOTED IN THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.R.F. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 2, 6, 7, 9, 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

8. Claim 1 recites the limitation "the targeted cell" in the fifth line. There is insufficient antecedent basis for this limitation in the claim.

9. Claim 2 recites the limitation "the particle" in the second line. There is insufficient antecedent basis for this limitation in the claim.

10. Claim 6 recites the limitation "the binding moiety" in the first and second line. There is insufficient antecedent basis for this limitation in the claim. It is unclear if applicant is referring to the first or second moiety mentioned in claim 4.

11. Claim 7 recites a Markush group consisting of "GALA, Helical erythrocyte lysing peptide, KALA and LAGA". It is unclear if KALA and LAGA are meant to be selected together (KALA and LAGA), or separately (KALA, and LAGA).

12. Claim 9 recites a Markush group consisting of "Amphotericin B, Alamethicin, Gramicidin, Melittin, Nigericin, P25, Polymixin B and Valinomycin and Vibriolsin". It is unclear if Polymixin B, Valinomycin, and Vibriolsin are meant to be selected together (Polymixin B and Valinomycin and Vibriolsin), or separately (Polymixin B, Valinomycin, and Vibriolsin).

13. Claim 17 recites the limitation "the human or animal body" in the last line. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

15. Claims 1, 10, 11, 14, 17 are rejected under 35 U.S.C. 102(e) as being anticipated by Meers et al [US 6,087,325].

Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 66 – column 2, line 20). In this situation, although the peptides are not defined as cytolytic by Meers et al, they do cause the rupture of the lipid vesicle in response to a predetermined metabolic signal which falls under the definition of cytolytic provided by applicant on p. 5, lines 18-21). Meers et al further teach that the liposomes of this invention can incorporate a species activated on modulation of permeability (column 9, lines 25-48), comprising one or more "bioactive agents," which are compounds or compositions of matter having biological, including therapeutic or diagnostic, activity in animals (column 9, lines 25-48).

16. With respect to claims 10 and 11, Meers et al teach that the species can be a dye or an enzyme (column 9, lines 25-48).

17. With respect to claim 14 and 17, Meers et al teach that the liposome can be used for diagnostic activity in animals (column 9, lines 25-29).

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. Claims 2-6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,339,069 B1] in view of Li et al [US 5,512,294].

Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 – column 2, line 20) and further incorporating a species activated on modulation of permeability (column 9, lines 25-48). Meers et al do not teach the use of antibodies as a binding agent for binding to an antigen on the cell type of interest. Li et al do teach the use of a binding agent that is a antibody for binding to an antigen on the cell type of interest (column 2, lines 58-68). Li et al further teach that the use of binding agents allow for specific targeting and attachment to desired cell surface molecules (column 4, lines 43-48). Therefore it would be obvious to use binding

agents, as taught by Li et al, in the method of Meers et al in order to allow for specific targeting and attachment to desired cell surface molecules.

20. With respect to claims 4 and 5, Li et al specifically teach the use of self-assembled aggregates of lipid molecules which offer great versatility in particle size and surface chemistry (column 4, lines 31-40).

21. With respect to claim 6, Li et al also teach the use of binding moieties such as biotin and avidin and their derivatives (column 4, lines 33-55, column 9, lines 9-21).

22. Claims 2-5, 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,339,069 B1] in view of Gibbons [US 4,829,011].

Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 – column 2, line 20) and further incorporating a species activated on modulation of permeability (column 9, lines 25-48). Meers et al do not teach the use of antibodies as a binding agent for binding to an antigen on the cell type of interest. Gibbons does teach the use of a binding agent that is an antibody for binding to an antigen on the cell type of interest (column 3, lines 6-24). Gibbons further teaches that agglutination assays do not require expensive detection equipment (column 1, lines 28-30). Therefore it would be obvious to use binding agents, as taught by Li et al, in the method of Meers et al in order to avoid expensive detection equipment.

23. With respect to claim 16, Gibbons teaches that the method of the present invention can be used with any type of sample that is capable of being used in an assay that relies on a specific binding reaction between members of a binding pair. The method is particularly useful for

biological samples but is not limited to such use. Industrial waste waters, natural waters, samples of air-borne particles, and industrial chemical reaction media can all be tested utilizing the present method (column 9, lines 36-48).

24. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,339,069 B1] in view of Wyman et al [Wyman et al, *Design, synthesis, and characterization of a cationic peptide that binds to nucleic acids and permeabilizes bilayers*, March 1997, Biochemistry, 36, 30008-30017].

25. Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 – column 2, line 20), as discussed above in paragraphs 15-17. Meers et al do not teach the use of a cytolytic peptide selected from the group consisting of GALA, Helical erythrocyte lysing peptide, KALA, and LAGA. Wyman et al, however, do teach the use of KALA to release entrapped aqueous contents from neutral and negatively charged liposomes (p.3008, col. 2, lines 22-33). Specifically, Wyman et al teach a method involving KALA-mediated release of entrapped aqueous contents from neutral and negatively charged liposomes (abstract). Wyman et al also teach that KALA is able to mediate significant and efficient gene delivery, transfection, and membrane leakage (p.3015, col.2, line 11 – p.3016, col.1, line 63). Therefore, it would be obvious to use KALA as a cytolytic peptide, as taught by Wyman et al, in the method of Meers et al, in order to mediate significant gene delivery.

26. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,339,069] in view of Parente et al [Parente et al, Mechanism of leakage of phospholipid vesicle contents induced by the peptide GALA, 1990, Biochemistry, 29, 8720-8728].

Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 – column 2, line 20), as discussed above in paragraphs 15-17. Meers et al do not teach the specific use of N, Myristic GALA as the cytolytic peptide. Parente et al do teach the use of GALA (p.8720, col.1, lines 12-26), and further teaches that once GALA assembles to form a pore or channel (lysing the lipid vesicle), leakage is rapid and complete (p.8726, col. 2, lines 4-17). Since the amino acid sequence is essentially the same, with similar functions and pH sensitivities, GALA would be functionally equivalent to N, Myristic GALA and therefore it would be obvious to utilize GALA or N, Myristic GALA, as taught by Parente et al, in the method of Meers et al, in order permit rapid and complete leakage when GALA lyses the lipid vesicles.

27. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,339,069 B1] in view of Rizzo et al [Rizzo et al, *Alamethicin incorporation in lipid bilayers: a thermodynamic study*, 1987, Biochemistry, 26, 2751-2759].

Meers et al teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 –

column 2, line 20), as discussed above in paragraphs 15-17. Meers et al do not teach the use of a cytolytic peptide selected from the group consisting of amphotericin B, alamethicin, gramicidin, melittin, nigericin, P25, polymixin B, valinomycin, and vibriolsin. Rizzo et al, however, do teach the use of alamethicin with phospholipid vesicles as conducting pores (p.2751, col. 1-2, p.2758, col. 1, lines 1-6). Rizzo et al further suggest the use of alamethicin as a "molecular switch" by means of aggregation in the membrane (p.2758, col. 1, lines 27-33). Therefore it would be obvious to use alamethicin with lipid vesicle particles, as taught by Rizzo et al, in the method of Meers et al, in order to introduce "a molecular switch" by means of aggregation in the membrane.

28. Claim 15 rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,339,069 B1] in view of Robinson et al [US 5,994,149].

Meers et al teach the use of lipid particles to detect pathogenic cells, as discussed above in paragraphs 15-17. Meers et al do not teach the detection of pathogenic cells in foodstuffs. Robinson et al, however, do teach the analysis of foodstuffs for pathogenic cells using liposomes (column 4, lines 19-24). Robinson et al further teach that it would be desirable to have a test kit that would eliminate operator error, and have a predictably accurate and reproducible rate of identification of pathogenic fungi, yeasts and molds (column 1, lines 16-45). Therefore it would be obvious to teach the detection of pathogenic cells in foodstuffs, as taught by Robinson et al, in the method of Meers et al, in order to have a test kit that would eliminate operator error, and have a predictably accurate and reproducible rate of identification of pathogenic fungi, yeasts and molds.

29. Claims 15 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meers et al [US 6,339,069 B1] in view of Blondin et al [US 4,808,517].

Meers et al teach the use of lipid particles to detect pathogenic cells, as discussed above in paragraphs 15-17. Meers et al do not teach the detection of pathogenic cells in water samples. Blondin et al do teach a method of using of lipid vesicles (column 4, lines 9-24) for the detection of toxins in water samples (column 8, lines 20-32) that is economical and efficient and can be quickly and easily performed (column 2, lines 64-68). Therefore it would be obvious to use the method of Meers to analyze water samples for pathogens as taught by Blondin et al, in order to detect toxins economically, efficiently, quickly and easily.

30. Claims 1, 2, 11-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Maxfield Wilson et al [US 5,776,487] in view of Meers et al [US 6,339,069 B1].

Maxfield Wilson et al teach the use of liposomes comprising a ligand capable of binding to a target analyte in a patient sample. Maxfield Wilson et al do not specifically teach the use of liposomes for detecting a cell type of interest present or potentially present in a sample, or the use of liposomes incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from the targeted cell. Meers et al, however, do teach a method comprising the steps of treating a sample with lipid vesicle particles incorporating a cytolytic peptide that modulates the permeability of the particles in response to a predetermined metabolic signal from a targeted cell type (column 1, line 60 – column 2, line 20). In this situation, although the peptides are not defined as cytolytic by Meers et al, they do cause the rupture of the lipid vesicle in response to a predetermined metabolic signal which falls under the definition of cytolytic provided by applicant on p. 5, lines 18-21). Meers et al also teach that

the liposomes of this invention can incorporate a species activated on modulation of permeability (column 9, lines 25-48), comprising one or more "bioactive agents," which are compounds or compositions of matter having biological, including therapeutic or diagnostic, activity in animals (column 9, lines 25-48). Meers et al teach that the liposomes can thus be used to treat mammals for diseases, disorders or conditions, e.g., tumors, microbial infection and inflammations, characterized by the occurrence of peptidase-secreting cells. Therefore it would be obvious to use liposomes incorporating a cytolytic peptide to detect a cell type of interest in order to treat mammals for diseases, disorders or conditions, e.g., tumors, microbial infection and inflammations.

31. With respect to claims 11-13, Maxfield Wilson et al teach the use of lipid particles containing a label selected from a group consisting of enzymes, radioisotopes, stable-free radicals, chemiluminescent compounds, bioluminescent compounds, pigments, fluorescent compounds, dyes and enzymes substrates. Maxfield Wilson et al further teach the use of a label that is an enzyme and the enzyme is selected from the group consisting of alkaline phosphatase and horseradish peroxidase (column 2, line 45 – column 3, line 27).

Conclusion

32. No claims are allowed.

33. The following references are also cited as art of interest: Carbonell et al [US 5,494,803], Adler Moore et al [US 5,874,104], Arab et al [US 6,482,586], Bally et al [US 4,885,172], Wong [US 6,468,558], Maxfield Wilson et al [5,780,319], Coffey et al [US 5,824,490], Chandraratna [US 6,627,652], Leippe et al [Leippe et al, *Pore forming peptide of pathogenic Entamoeba*

histolytica, 1991, Proc Natl Acad Sci, 88, 7658-7663], Trubetskaya et al [Trubetskaya et al, *Monoclonal antibody to human endothelial cell surface internalization and liposome delivery in cell culture*, 1988, FEBS letters, 228, 131-134], and Matsuzaki et al [Matsuzaki, et al, Pore formation and translocation of melittin, August 1997, Biophys J, 73, 831-838].

34. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nelson Yang whose telephone number is (703) 305-4508. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V Le can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

NY

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
11/16/03